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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Harry A. Dugger, III, et al.

Application No.: 10/671,715 Confirmation No.: 9275

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For: BUCCAL, POLAR AND NON-POLAR SPRAY CONTAINING ZOLIPIDEM Examiner: M. Haghighatian

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF FRANK E. BLONDINO, PhD. UNDER 37 CFR 1.132

Dear Sir:

I, Dr. Frank E. Blondino, declare and state as follows:

1. I am of legal age, and under no disability that prevents me from attesting to the following statements and information, which are based on my personal knowledge and observations or on my best information and belief.

2. I am Executive Director of Formulation and Process Development for NovaDel Pharma Inc., the assignee of U.S. Patent Application 10/671,715 (the "'715 application"). My responsibilities as Executive Director of Formulation and Process include overseeing and developing formulations for various pharmaceutical compositions, including buccal spray compositions.

3. I have read and understand the claims and specification of the '715 application.

4. Further, I am familiar with pharmacokinetic/pharmacodynamic studies designed to evaluate overall comparability of the pharmacokinetic profile of a zolpidem oral spray and AMBIEN® tablets as determined by Cmax and AUCs. The studies' objectives also included comparative evaluation of metrics of the speed of drug absorption and pharmacodynamic properties of the zolpidem oral spray as well as evaluation of its safety and tolerability profile.

5. Data from the studies is provided in Exhibit A hereto. As shown by the data, the zolpidem oral spray was surprisingly effective and superior to administration by oral tablet.

6. The oral spray groups demonstrated consistently faster drug absorption than the tablet groups as evidenced by higher concentration levels and AUCs at early post-dosing time points. The primary metric of the speed of drug absorption (percentage of subjects reaching therapeutic drug levels of at least 20 ng/mL by 15 minutes post-dosing) revealed statistically significant superiority of the oral spray groups ($p < 0.001$) when compared to the same doses of oral tablets. Notably, in the first study 64% of subjects achieved this drug level after receiving 5mg oral spray vs. 24% of subjects dosed with 10mg AMBIEN® tablet. This treatment difference was also highly significant ($p= 0.0005$). Thus, the oral spray shortens the time to onset of therapeutic action of sleep latency as compared to a tablet. Importantly, from the stand point of safety, the mean maximum plasma concentration (Cmax) and bioavailability, as measured by the area under the curve, achieved during the entire 12-hour observation period for the 10mg oral spray did not exceed that of the oral tablet.

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. All statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified patent.

Date: Sept 28, 2007 By: _____

Dr. Frank E. Blondino

EXHIBIT A

Clinical Studies

The first, single-center study using 45 healthy male and female volunteers was a randomized, 4-way crossover, open-label, dose-ranging study (Study 1). This study compared 5mg and 10mg doses of zolpidem oral spray to the same doses of AMBIEN® tablets. The second, single-center study using 24 elderly healthy male and female volunteers was a randomized, 2-way crossover, open-label, pharmacokinetic (PK)/pharmacodynamic (PD) study of the 5mg zolpidem oral spray and 5mg AMBIEN® tablet (Study 2). The study zolpidem spray formulation was as follows:

Component	Percent (w/w)
Zolpidem tartrate, EP	4.66
Citric acid monohydrate, USP	9.57
Neotame®	0.01
Hydrochloric acid, NF	0.63
Propylene glycol, USP	35.00
Benzoic acid, USP/EP	0.05
W.S. artificial cherry flavor	0.25
Purified water, USP	49.83

Both pharmacokinetic/pharmacodynamic studies were designed to evaluate overall comparability of the pharmacokinetic profile of the zolpidem oral spray and AMBIEN® tablets as

determined by Cmax and AUCs. The studies' objectives also included comparative evaluation of metrics of the speed of drug absorption and pharmacodynamic properties of the zolpidem oral spray as well as evaluation of its safety and tolerability profile.

Data from the both studies indicate overall comparability of pharmacokinetic profile of zolpidem oral spray when compared to the AMBIEN® tablet. This assessment is based on the evaluation of the maximum concentration level, Cmax, and areas under the drug concentration curves, AUCs, to the last measurable observation and extrapolated to the infinity. Data from the two studies suggest that zolpidem oral spray is bioequivalent to the AMBIEN® tablet.

In a 4-way crossover study in 45 healthy volunteers, 64% of patients receiving 5mg zolpidem oral spray and 78% of subjects receiving 10mg zolpidem oral spray, reached therapeutic drug levels (>=20ng/mL) by 15 minutes post-dosing. Results for zolpidem oral spray were statistically significantly higher when compared to 5mg and 10mg oral tablets with only 18% and 24% of the subjects, respectively, reaching therapeutic drug levels for the same 15 minute post-dosing period. Plasma zolpidem concentrations were determined by LC/MS/MS separation with consecutive detection. The results of the 4-way crossover study are shown in Tables I and II below and FIGS. 1-3.

In a 2-way crossover study in 24 geriatric volunteers (subjects older than 65 years), results were also statistically significantly higher in 5mg zolpidem oral spray group when compared to the 5mg oral tablet with 79% of subjects reaching therapeutic drug levels by 15 minutes post-dosing versus 29% achieving therapeutic results for the same timeframe with oral tablets. The results of the 2-way crossover study are shown in Tables III and IV below.

Evaluation of the primary pharmacodynamic endpoint, defined as the change in the Digit Symbol Substitution Test (DSST) score from pre-dosing baseline to the 13 minutes post-dosing, in both studies also revealed statistically significant superiority of the oral spray when compared to the oral tablets. Notably, 5mg zolpidem oral spray demonstrated faster and stronger initial pharmacodynamic effects when compared to 10mg AMBIEN® tablets. Importantly, observed differences in the pharmacokinetic and pharmacodynamic metrics of drug absorption were not associated with increase in the overall exposure to the study drug: maximum concentration level (Cmax) and areas-under-the-curve (AUCs) were comparable between zolpidem oral spray and AMBIEN® tablets. Data from these two studies suggest that zolpidem oral spray is bioequivalent to the AMBIEN® tablets.

The oral spray groups demonstrated consistently faster drug absorption than the tablet groups as evidenced by higher concentration levels and AUCs at early post-dosing time points. The primary metric of the speed of drug absorption (percentage of subjects reaching therapeutic drug levels of at least 20 ng/ml by 15 minutes post-dosing) revealed statistically significant superiority of the oral spray groups ($p < 0.001$) when compared to the same doses of oral tablets. Notably, in the first study 64% of subjects achieved this drug level after receiving 5mg oral spray vs. 24% of subjects dosed with 10mg AMBIEN® tablet. This treatment difference was also highly significant ($p= 0.0005$). Thus, the oral spray shortens the time to onset of therapeutic action as compared to a tablet.

In both studies, researchers administered the Digit Symbol Substitution Test, DSST (twice before dosing and at 13 and 23 minutes post-dosing) and 12-item Visual Analog Scale (twice

before dosing and at 12 and 22 minutes post-dosing) to all participants. The DSST is a complex test, and a reduction in DSST score is considered an indicator of sleepiness and sedation. Change in the DSST from pre-dosing baseline to 13 minutes post-dosing was pre-specified as a primary pharmacodynamic endpoint in both studies. Statistically significant treatment differences were observed for this endpoint. In the first study, 5mg oral spray was statistically significantly superior when compared to the 10mg AMBIEN® tablet.

Importantly from the stand point of safety, the mean maximum plasma concentration (Cmax) and bioavailability, as measured by the area under the curve (AUC), achieved during the entire 12-hour observation period for the 10mg oral spray did not exceed that of the oral tablet.

Table I: Study 1 BE Results

Parameter	**5 mg AMBIEN Tablet N= 44**	**5 mg Zolpidem OS N= 44**	**10 mg AMBIEN Tablet N= 44**	**10 mg Zolpidem OS N= 44**	**Ratio LS/Tablet (1) 5mg (2) 10 mg**	**90% Conf Intervals (1) 5mg (2) 10 mg**
Cmax (ng/mL) LS Mean	114.1	101.1	206.8	193.0	(1) 0.889 (2) 0.933	(0.788 – 1.003) (0.854 – 1.020)
AUC(0-T) [h*(ng/mL)] LS Mean	398.0	351.4	755.2	707.0	(1) 0.883 (2) 0.936	(0.789 – 0.991) (0.861 – 1.016)
AUC(0-∞) [h*(ng/mL)] LS Mean	428.7	379.3	822.9	769.3	(1) 0.885 (2) 0.935	(0.789 – 0.988) (0.863 – 1.016)

AUC(0-T) calculated by the linear trapezoidal method
AUC(0-∞) AUC(0-T) + ($0.693/K_e$)

Table II: Study 1 Primary PK and PD Endpoints

Parameter	**5 mg AMBIEN Tablet N= 44**	**5 mg Zolpidem OS N= 44**	**10 mg AMBIEN Tablet N= 44**	**10 mg Zolpidem OS N= 44**	**P-Value (Test)**
Percentage of Subjects Reaching Ther Level (>= 20 ng/mL) by 15 Min	18.2%	63.6%	24.4%	77.8%	P <0.001 for all comparisons (5 mg and 10 mg LS vs 5 mg and 10 mg Tab) (McNemar's test)
Change in DSST score from pre-dosing baseline to 13 Min Mean ± SD Median	-3.1 ± 7.6 -1.5	-7.7 ± 8.5 -6.5	-3.3 ±8.5 -1.5	-13.6± 13 -11.5	P<0.05 For all comparisons (5 mg and 10 mg LS vs 5 mg and 10 mg Tab): (Wilcoxon Signed Rank, Rank ANOVA

Table III: Study 2 Major PK Parameters

Parameter/ Statistic	**5 mg AMBIEN Tablet** **N= 24**	**5 mg Zolpidem OS** **N= 24**
Cmax (ng/mL) Mean ±SD Median Range	 133.7 ± 51.8 125.9 53-268	 127.8 ± 38.4 125.4 52-189
AUC(0-T) [h*(ng/mL)] Mean ±SD Median Range	 457.5 ± 180.3 425.3 187-975	 432.8 ± 180.8 408.3 159-913
AUC(0-∞) [h*(ng/mL)] Mean ±SD Median Range	 493.0 ± 213.2 447.4 192-1112	 465.3 ± 212.1 423.4 161-1042

AUC(0-T) calculated by the linear trapezoidal method
AUC(0-∞) AUC(0-T) + ($0.693/K_e$)

Table IV: Study 2 PK and PD Endpoints

Parameter	**5 mg AMBIEN Tablet N= 24**	**5 mg Zolpidem OS N= 24**	**P-Value (Test)**
Percentage of Subjects Reaching Ther Level (>= 20 ng/mL) by 15 Min	29.2%	79.2%	P=0.0005 (McNemar's test)
Change in DSST score from pre-dosing baseline to 13 Min Mean ± SD Median	 0.5 ± 7.8 1.5	 - 5.4 ± 9.3 -3.3	P=0.0352 (Wilcoxon Signed Rank) P=0.116 (ANOVA)P=0.0332 (Rank ANOVA)